REMARKS

Claims 1-85 are pending in the above-identified application and are currently under examination. Applicants have reviewed the office action mailed May 21, 2003, and respectfully traverse all grounds of rejection set forth therein.

The drawings have been objected to allegedly because Figures 1 and 3 contain shading which obscures detail and because Figure 1 allegedly contains handwritten characters that are difficult to read.

Attached as Exhibits A - C are proposed drawing corrections. Applicant points out that the characters underneath the axis in Figure 1 correspond to mathematical nomenclature and are not handwritten. This nomenclature is maintained in the proposed drawing correction only it has been enlarged for clarity. With respect to the assertions of shading regions, Figure 1 is a plot of several mathematical criteria. Applicants are unaware of any shading in this Figure. The shaded area of Figure 3 has been removed. As with Figure 1, the proposed correction to Figures 2 and 3 other than that described above is to enlarge the Figure as shown in the attached Exhibits. Applicant respectfully requests approval of the proposed drawing corrections

Rejections Under 35 U.S.C. §112

Claim 1-85 stand rejected under 35 U.S.C. §112, first paragraph allegedly for lacking enablement. In this regard, the office action appears to concede that the claims are enabled for determining the true signal of an analyte using microarrays but further asserts that the specification does not provide enablement for the determination of a signal in any situation.

Applicant contends that the application sufficiently supports the full scope of the invention as claimed. To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997), *see also* MPEP §2164.01(c), fourth paragraph. Further, in *Johns Hopkins Univ. v.*

CellPro, Inc., 152 F.3d 1342, 1360 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. (*citing PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996); *see also In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988)).

The claimed invention is directed to a method of determining a true signal of an analyte. The method consists of measuring an observed signal for one or more analytes and determining a mean signal (μ) and a system parameter (β) for the analyte that produce a probability likelihood of the observed signal. The observed signal is related to the mean signal by an additive error (δ) and a multiplicative error (ε) and the system parameter (β) specifies the properties of the additive and multiplicative errors (δ, ε). The application teaches throughout the relationship of these parameters including, for example, in the definitions at pages 6-8; the exemplary applicability of the claimed methods to a variety of samples and systems, at pages 11-16, and, for example, the specific relationships described at pages 17-33, and exemplified further in the Examples.

The application further teaches throughout how to determine the true signal from any of a variety of observed signal. For example, page 11, lines 22-28, the application expressly teaches that the method of the invention are applicable to "measure any analyte that serves as a sample or is contained in a sample so as to allow for detection of the presence of the analyte." The application further teaches, for example, at page 12, line 12 through page 15, line 4:

The methods of the invention are applicable to the measurement of analytes and determination of true signals in both biological and non-biological settings. For example, in a biological setting, experimental error can be classified into at least two categories. Biological

error is one such category and consists, for example, of intrinsic error introduced by the biological components. In this regard, regulation at both the gene expression and protein activity levels can be substantially altered due to apparent negligible experimental differences in the treatment of a biological sample. A specific example is where gene expression changes due to the use of different batches of the same media during the course of an experiment. Such biological error produces measurable differences in the level of an analyte such as an expressed gene.

Another category is the extrinsic error introduced through experimental manipulation. For example, differences in sample preparation, analyte or probe labeling efficiency, hybridization or binding conditions, synthesis of probes, batches of solid-phase substrate and detection efficiency introduce variations in the determination of a measured analyte, even though all components and processes can be controlled so as to result in apparent negligible differences. Nevertheless, measurable differences in observed analyte signal occur due to the introduction of such error.

Similarly, for non-biological settings the methods of the invention are applicable for determination of true signals from measured analytes in essentially any process or steps thereof for which a quantitative determination or comparison of a measurable component is desired.

The above exemplary, and other forms of error all affect the perceived amount of a measured analyte through the introduction of fluctuations in the observed signal. Assessing the true signal of the analyte, independent of such fluctuations, allows direct comparison of analyte levels. Moreover, because the true signal of an analyte measurement can be determined, the methods of the invention provide a means for a direct or standardized comparison of analyte measurements both within an experimental system and between different systems. Given the teachings and guidance provided herein, essentially any analysis format known in the art can be used for such subsequent comparison of analytes once the true or mean signals are obtained. Therefore, the methods of the invention can be used to accurately and reproducibility determine the true signal of essentially any measurable analyte as well as used for the initial step in, for

example, a comparative analysis of the same analyte under different conditions, the same analyte under repetitive conditions or different analytes under the same conditions.

As will be described further below, it is understood that the methods of the invention are equally applicable to both large and small sets of analyte samples and sets of measurements. Determination of the true signal for an individual sample is performed similarly as that for the determination of many, and even hundreds or thousands of samples. Similarly, the comparison of true signals for determination of relative amounts of an analyte between samples also is performed for two samples as it is for comparison of many sample pairs or higher order sets of multiple comparisons. Therefore, given the teachings and guidance provided herein, the number of true signals that can be simultaneous determined, or sets of samples that can be simultaneously compared for relative amounts of true signal is only limited by the available computational power.

The methods of the invention for determining the true signal of an analyte can be applied to a variety of situations. For example, repeated measurements of the observed signal such as intensity x for one or more analytes can be obtained and subsequently used in the method of the invention to characterize the error and determine the significance value for each observed signal. For example, repeated observations of the signal associated with a single analyte such as, for example, the observed intensity of a single gene in a microarray, can be utilized in the methods of the invention to monitor, for example, the variation introduced by two or more distinct conditions, the total error introduced over a given time or sporadic error introduced by any means including variation caused at any step in the protocol.

The above teachings are exemplary of that which can be found throughout the application. The application teaches multiple uses for the claimed invention including both biological and non-biological settings and expressly teaches that the methods are applicable to the measurement of any analyte that can be detected. Accordingly, the application sufficiently enables the invention as claimed and withdrawal of this ground of rejection is respectfully requested.

Claims 1-85 also stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for use of the term "true signal." In this regard, the office action appears to assert that the use of the term true signal differs from the meaning of the value that is measured in the claimed method.

The application teaches, for example, at page 12, lines 1-11, that "[t]he true signal of an analyte is independent of experimental variation or error introduced prior to or during detection of the observed signal" and that the "mean signal of an analyte is a measurement of the true or actual level of that analyte." Therefore, the application relates the mean signal to a true signal because it teaches that the mean signal is a measurement of the true signal as described and claimed in the application. Accordingly, the invention is sufficiently definite as described and claimed in the application to allow those skilled in the art to practice the invention as claimed. Applicants respectfully request withdrawal of this ground of rejection.

Rejections Under 35 U.S.C. §102

Claims 1-85 stand rejected under 35 U.S.C. §102 (b) as anticipated by Stark et al., U.S. Patent No. 5,568,400, allegedly because Stark et al. describes all the elements of the claimed invention. In this regard, the office action asserts that Stark et al. describes methods of detecting analytes where average and mean data are obtained; additive and multiplicative error coefficients are calculated; multivariate estimation methods are used to determine corrections; modeling by maximum likelihood regressions and that the equations of Stark are the same or slight rearrangements of those set forth in the application.

When lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims. *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, (Fed. Cir. 1998) (quoting *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544-45, 24 U.S.P.Q.2d 1133, 1136 (Fed. Cir. 1992)). To establish a *prima facie* case of anticipation, the Examiner must show that the single reference cited as anticipatory art describes all the elements of the claimed invention.

Applicants claim a method of determining a true signal of an analyte. The method consists of measuring an observed signal for one or more analytes and determining a mean signal (μ) and a system parameter (β) for the analyte that produce a probability likelihood of the observed signal. The observed signal is related to the mean signal by an additive error (δ) and a multiplicative error (ε) and the system parameter (β) specifies the properties of the additive and multiplicative errors (δ, ε).

The office action fails to particularly point out each of the elements claimed by in the invention that are allegedly described in Stark et al. Instead, the office action provides an assertion that the cited reference anticipates the claimed invention and points to the use of maximum likelihood regressions and an apparent similarity of equations in Stark et al. However, the office action fails to show that Stark et al. either describes a system parameter (β) as described and claimed in the subject application or that such a system parameter, if described in Stark et al., is the same system parameter (β) as described an claimed in the subject application. Absent a showing that Stark et al. describes a system parameter that specifies properties of the additive error (δ) and the multiplicative error (ε) as claimed in the application, the office has not satisfied its burden. Therefore, the cited reference cannot anticipate the claimed invention and withdrawal of the rejection is respectfully requested.

Claims 1-85 also stand rejected under35 U.S.C. §102 (a) as allegedly anticipated by Ideker et al. Applicants have submitted a declaration upon the filing of this application averring that they are the joint inventors of the claimed invention. Dr. Hood provided the impetus and laboratory support for the scientific project and as such was listed as a co-author of the Ideker et al. publication. Accordingly, Ideker et al. is not a publication by another and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

Respectfully submitted,

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